day; 20 to 50 c.c. of fluid are withdrawn and 15 to 30 c.c. of serum injected by gravity. The serum should be warmed to body temperature and a smaller amount always reinjected than the amount of fluid withdrawn. Three assistants are generally necessary to carry out the operation carefully and safely.

5. The interval of time between the punctures and the total number of punctures will depend upon the rapidity in the reaccumulation of the fluid, as indicated clinically by the reappearance of a bulging anterior fontanelle and upon the result of the bacteriological culture of the ventricular fluid.

6. A lumbar puncture should be made at the time the patient is discharged from the hospital in order to determine the reëstablishment of the communication between the ventricular cavities in the brain and the subdural space in the spinal canal.

7. If the baby is breast-fed every effort should be made to have the breast feeding continued while the patient remains in the hospital.

8. Occasionally the diagnosis may be assisted in cases giving a dry tap, and before deciding upon a ventricular puncture, by making a culture of the nasal discharge and finding the meningococcus present.

9. Cases of posterior basilar meningitis should be followed up for a period of years to determine the final outcome in those who recover after ventricular punctures and injections of antimeningitis serum.

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PRIMARY CARCINOMA OF THE GALL-BLADDER: AN ANALYSIS OF TWENTY-THREE PROVED INSTANCES OF THE DISEASE.[1]

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In the series of 1000 operatively and pathologically demonstrated instances of gall-bladder disease which I reviewed a year

[1] Read at the Twenty-third Annual Meeting of the American Gastro-enterological Association, Atlantic City, N. J., May 6 and 7, 1918.

since,[2] there occurred 31 cases of malignancy (3.1 per cent.). Of these gall-bladders the neoplasm was primary in 23. In the remaining 8 cases the gall-bladder was secondarily invaded by extension of malignancy from adjacent viscera. There occurred no instance of primary neoplasm of the bile ducts. It is thus evident that of a large series, including gall-bladder affections of nearly every type, primary malignancy arose in 2.3 per cent. The practical value of this rate of the incidence of gall-bladder neoplasms is indicated by the observation that it is more than four times the frequency of primary malignancy of the appendix, and that of neoplasms involving the organs concerned with digestion the gall-bladder is involved fifth in frequency (1 of stomach; 2 of colon and cecum; 3 of rectum; 4 of esophagus; 5 of gall-bladder; 6 of liver; 7 of appendix).

It is frequently stated that the diagnosis of primary malignant disease of the gall-bladder is not difficult. This statement holds true for instances in which there is extensive involvement when pronounced general constitutional upset has occurred and in which the prognosis is evident to even a layman. That there are actual difficulties concerned with the accurate diagnosis of primary neoplasm of the gall-bladder is proved by the fact that of the 23 cases in my series in but 7 instances (30.4 per cent.) was the unqualified, prelaparotomy diagnosis correctly made and recorded in the histories and operation cards. In no case in which early well-localized gall-bladder malignancy existed was there a correct preoperative diagnosis. It would seem, consequently, that the clinical diagnosis of curable neoplasm of the gall-bladder occupies a status relatively similar to that of the clinical diagnosis of early curable primary gastric malignancy.

On account of the foregoing observations it is considered that a clinical analysis of the 23 instances of primary gall-bladder malignancy included in my series of established gall-bladder disease will not be altogether valueless.

Sex. It is commonly recorded that females are affected approximately three times as frequently with malignant disease of the gall-bladder as are males. (Musser, Zenker, Siegert, Mayo, Moynihan and others.) From this observation it is usually deduced that because the incidence of gall-stones in females is about three times that in the male, gall-stones must of necessity be the cause of gall-bladder neoplasms. In spite of many successful experiments in the production of gall-stones there is no instance on record in which the deliberate experimental production of the calculi nor the accidental arising of such a consequence of foreign body (ligatures, drains, etc.), resulted in malignant disease, and this in spite of the fact that the so-called "irritant" has lain even for years in a pre-

[2] Smithies, Frank: Proceedings of the Section in Medicine, American Medical Association, New York Session, June 7, 1917.

viously healthy or diseased gall-bladder. (Homans, Jacques, Meyer, Mignot.)

In our series of primary malignancy of the gall-bladder there were 16 males and 7 females.

AGE. The average for my series was for both sexes 59 years. The minimum age in males was 44 years, the maximum 76 years (average 57.9 years). In females the minimum age was 56 years and the maximum 72 years (average 62.2 years). It would seem that in spite of the greater prevalence of gall-stones in the female the average age at which malignant disease of the gall-bladder occurs is more than five years later than in the male.

HEREDITY. There was only one patient of the series in whom a definite blood relationship of malignancy could be elicited. In another patient the husband had died about a year previously from cancer of the stomach.

DURATION OF SYMPTOMS. In the 100 cases of cancer of the gall-bladder which Musser[3] collected from various non-related sources and from the literature in 1889 the average duration of the ailment is stated as six and two-third months, with a minimum duration of seven weeks and a maximum of four years. It is quite evident when one analyzes cases that in numerous instances the patient has been affected with a gall-bladder dyspepsia of two distinctly definite types, viz.: (*a*) a clinical form, not that commonly considered malignant, and (*b*) a terminal complaint frequently evidencing such serious local and constitutional disturbances as to render a suspicion of some malignant process highly probable. There were in my series 16 cases (69 per cent.) in which a previously harmless type of gall-bladder dyspepsia had been followed by an alarming complaint. In the early period the ailment was commonly intermittently manifested and extended in the average over 9.6 years (minimum 3 years; maximum 36 years). The terminal phase of the disease was one of continuous malfunction (often, clinically, on the part of the gall-bladder) and in duration averaged 10.3 months (minimum 5 weeks, maximum 3 years).

Of the 7 cases in which from its inception the affection had been of an obstinate and progressive type the duration averaged 3.4 months, (minimum 6 weeks, maximum 6 months).

It would seem that consideration of these two types of dyspepsia ultimately proved to be associated with malignant disease of the gall-bladder might furnish more than a clinical hint relative to the nature of the ailment and might also throw considerable light, etiologically, upon the relationship existing between chronic gall-bladder irritation (infective, chemical, foreign body, *e. g.*, calculi) and gall-bladder irritation. It should be here emphasized that chronicity, histologically speaking, must be differentiated from

[3] Boston Med. and Surg. Jour., December 5, 1889, No. 23, cxxi, 553.

chronicity, indicating months or years' duration of disease: a powerful continuously acting stimulus may be quite capable of producing histological changes of malignancy quite as marked as those occurring when an intermittently acting or weakened agent has been manifest over a long period of time.

SYMPTOMATOLOGY. In 17 patients the early history of the affection indicated rare or frequent attacks of such dyspepsia as is commonly associated with catarrhal cholecystitis or cholelithiasis. Not rarely these attacks had borne definite relationship to an acute infectious disease. The history of typhoid fever was obtained from 12 patients—pneumonia from 3 and malaria from 1. At the time of their coming to the hospital, in 20 instances the patients were affected with a continuous and disabling ailment. The characteristics of this ailment now will be considered.

APPETITE. In 14 patients (60.8 per cent.) there was persistent anorexia. The food desire was lessened in 5, but well maintained and in nowise abnormal in 4.

WEIGHT LOSS. There was but one patient who had maintained normal weight. In this case early exploration to relieve distressing gall-bladder dyspepsia disclosed small sessile papilloma. In the remaining 22 cases of my series, weight loss, generally associated with physical weakness, averaged 28 pounds (minimum 15 pounds, maximum 60 pounds). The weight loss was frequently astonishingly rapid, and of itself when taken in connection with an ailment clinically dependent upon gall-bladder malfunction should have furnished a significant hint relative to the development of neoplasm. In three months one patient lost 40 pounds, another 60 pounds in seven months and a third 28 pounds in five weeks. It was not unusual for persistent weight loss associated with unaccountable anorexia weakness or diarrhea to cause alarm a considerable time before symptoms or signs of gall-bladder anomaly presented. Five patients came for the examination at which malignancy was discovered on account of the persistent and puzzling loss of weight.

BOWELS. In 11 cases distressing constipation was recorded; in 4 stools of normal frequency, while 8 patients were subject to diarrhea not rarely uncontrolled by diet and commonly exhausting. Nocturnal diarrhea, with disturbance of sleep and rest, seemed to be an important influence in causing rapid weight loss and cachexia. This was especially noticeable when the gall-bladder malignancy had invaded the pancreas (6 cases).

STOOLS. There were no abnormal findings in 8 instances. The stools of the remaining 15 patients persistently or intermittently indicated interference with free bile flow. They were definitely acholic in 9 cases.

BILE PIGMENT IN THE URINE. Bile pigment in the urine as shown grossly by dark sherry-colored urine, capped with thick green brown or olive froth or by chemical test, was present in 11 instances.

The urine analyses of 5 patients returned report "suspicious" for bile coloring.

(*g*) JAUNDICE. This was definitely manifested by 14 patients. In 3 patients the jaundice was intermittently present. In 11 patients the jaundice was persistent. In these cases the skin coloration and the sclerotic tinting ranged from lively greenish-brown to a muddy or dusky olive green. Itching of the skin or distressing anal pruritus was obstinate in 7 of the continuously jaundiced patients. Such itching was often of significant importance with respect to loss of sleep and rapidly developing weakness.

(*h*) FEVER. Although Musser concludes that in malignancy of the gall-bladder the temperature is liable to be subnormal, rise in temperature with or without chilly sensations or sweats was recorded in 5 patients of my series. Its character was similar to that of cachectic processes associated with malignancy in general or with such exhausting ailment as progressive tuberculosis, viz., a subnormal morning temperature with a rise toward evening or upon unwonted physical or mental exertion. The maximum temperature recorded was 102.3°. In one instance of indefinite upper abdominal nodular tumor not associated with jaundice or pain, the character and persistence of the fever led to a preoperative diagnosis of tuberculosis of the peritoneum. In the presence of ascites, such mistake in diagnosis is not easily avoided unless there be careful scrutiny of the patient's history previous to the period of his presenting complaint.

PAIN. Some degree of abdominal discomfort was experienced by 21 patients (91.2 per cent.). There was severe pain in 16 cases (69 per cent.). In 5 cases sharp, prostating colic-like attacks of pain required opiate relief. In 2 patients the character of the pain suggested gall-bladder perforation.

The abdominal distress was *continuous* in 14 cases but only *intermittently* manifested in 7. It was not unusual to note aggravations of pain, even of colic-like degree, in those patients in whom a continuous abdominal discomfort had been experienced.

Location of Distress. Eleven patients complained of general epigastric pain; in 5 discomfort was definitely confined to the right upper abdominal quadrant, in 1 each distress at the right costal arch, the region of the navel and the xiphoid. In 2 instances there was generalized liver region pain, with a point of intensity below the tip of the right scapula.

Transmission of Pain. There was persistently referred pain in 14 cases. In the order of frequency, pain transmission occurred to the right back, the right shoulder, the tenth to twelfth dorsal vertebræ and the midepigastrium. Distress at the referred point was not infrequently more annoying than was that experienced at the zone of pain inception.

Time of Pain. Maximum distress was commonly recorded as occurring shortly after the taking of food, upon sudden changes of position or after jolting or jarring (*e. g.*, after a rise over a rough road). Only 2 patients complained of severe night pains.

Relief of Pain. In 8 instances opiates were required to make the patient comfortable. Fasting, vomiting, free catharsis, gastric lavage or the administration of alkalies were commonly helpful agents.

ABDOMINAL TENDERNESS. This was recorded in 22 of the 23 cases. It was usually in the right upper quadrant or in the epigastrium generally. In 7 instances the tenderness was so exquisite as to suggest gall-bladder perforation with protective peritonitis.

ABDOMINAL TUMOR. Such was definitely determined or indefinitely delimited in 17 cases (74 per cent.). The tumor or ridge commonly occupied the right upper abdomen. In 4 cases it extended well across the epigastrium. In size the tumor ranged from a finger-like ridge to an oval or pear-shaped mass as large as a grapefruit. Its *consistency* was commonly firm, although in 3 instances there was a cystic feel, with a suggestion of fluctuation. Its *surface* was definitely rough or nodular in 9 cases. The tumor was *movable* on respiration or change of position in 4 instances. In the remainder the mass seemed deeply fixed. *Tenderness* over the tumor was noted in 12 patients.

ENLARGEMENT OF THE LIVER. Enlargement of the liver occurred in 11 patients (46 per cent.) of the entire series and in 8 cases (47 per cent.), in which abdominal tumor was coincident. In degree the liver enlargement ranged from the organ's being just palpable to its extension downward as much as 5½ inches below the right costal limit. Of the 11 patients in whom the liver was enlarged there was palpable hepatic nodulation in 4. The liver consistency was commonly very firm: in fact, so firm as to suggest the diagnosis of interstitial cirrhosis. Two patients were brought under observation with such previous diagnosis. In 1 case there was concomitant splenic enlargement.

ASCITES. This was demonstrated in 3 patients (13 per cent.) before laparotomy. In 2 other patients free abdominal transudate was discovered at operation (ascites 21.7 per cent., for the series). Pressure upon or actual malignant invasion of the portal vein or its radicles commonly produced the ascites. In 1 instance there was involvement of the receptaculum chyli and the thoracic duct with a resultant chylous ascites.

BELCHING AND NAUSEA. Belching and nausea were annoying in 17 patients. With these symptoms a distressing sensation of upper abdominal "crowding" or "up pressure," particularly at night or after eating, was sufficiently uncomfortable to prevent adequate feeding or uninterrupted sleep.

VOMITING. This occurred either as a daily or an irregular event in 18 patients (79 per cent.). Vomiting of retained food was observed in 10 patients. The vomitus of 13 patients was persistently bile-stained. In 3 cases in which obstruction occurred near the papilla of Vater the vomitus was persistently colored with muddy brown bile. In these cases the gastric extracts grossly suggested those commonly to extensive malignant stenosis of the pyloric end of the stomach.

TEST-MEALS. Data is available in 12 cases. Persistent twelve-hour food retention existed in 5 cases. The *average free HCl* was 21 (minimum 4, maximum 56). There were 6 instances of achlorhydria. The *average total acidity* was 30.1 (minimum 4, maximum 64). *Chemical test* for blood pigment was positive in the gastric extracts from 6 patients. *Lactic acid* was recorded in 5 cases.

Microscopically. Yeasts were in excess in 5 cases and *sarcinæ* coincident in 4. Organism of the Boas-Oppler type were present in 3 of the achlorhydria gastric contents where there was associated food-stagnation.

ROENTGEN FINDINGS. There were 11 cases in which roentgen examination had been made before laparotomy. In 5 cases roentgen-ray plates demonstrated atypical shadows in the gall-bladder zone strongly suspicious for calculi. In 3 cases there was interference with the emptying of the stomach, the barium meal remaining longer than six hours in the gastric cavity. In 1 case there was a filling defect at the outlet of the stomach, which, interpreted in the light of the clinical symptomatology and the test-meal examinations, appeared to result from pyloric cancer. At fluoroscopy, the roentgen examination not rarely proved of service in demonstrating that the palpable abdominal tumor lay outside the stomach or other portions of the alimentary tract. There was 1 instance in which the malignant gall-bladder involved the hepatic flexure of the colon. In this case there was not only a colon filling defect but also marked retardation in the progress of colon contents caudad.

OPERATIVE FINDINGS. 1. *The Neoplasm.* In 4 cases the malignant change was well defined and located in the fundus or body of the gall-bladder. In 2 cases there were malignant papillomata. In the remaining 17 cases there was extensive neoplastic involvement of the entire gall-bladder, with contiguous invasion of adjacent viscera.

2. *Histologically* the lesion was constantly carcinoma of the columnar or spheroidal cell type.

3. CONCOMITANT INCIDENCE OF GALL-STONES. Of the 23 instances of primary malignancy of the gall-bladder, cholelithiasis was an associate finding in 16 patients (69 per cent.). In the remaining 7 patients it was not possible to prove the previous presence of gall-stones, although in 4 cases the early histories suggested such. The relationship of cholelithiasis to malignant disease has already been commented upon. It would appear that the fact that gall-stones are often found

in malignant gall-bladders furnishes evidence worthy of note with respect to the gall-stones acting as sources of irritation and the production of malignant hyperplasia of the gall-bladder mucosa. It is not impossible, however, that in malignant gall-bladders calculi may form as a consequence of cancerous change altering the excretory function of the gall-bladder mucosa or preventing proper emptying of the viscus. From the clinical histories of many patients who later on are shown to have malignant disease of the gall-bladder, attacks simulating gall-stones can be elicited at a time previous to the more recent ailment which is apparently clinically malignant. It would certainly seem that in patients in whom gall-stones can be proved to exist, from the clinical or special examinations, their early removal, together with the gall-bladder, might be a considerable factor in preventing malignancy in the individual and also in the human family.

4. Involvement of Adjacent Viscera. In 11 cases the lymph nodes showed metastases; in 8 cases the liver was extensively invaded; in 6 the pancreas; in 2 the stomach and in 1 case each there was extension to the omentum, the hepatic flexure of the colon and the retroperitoneal lymph tissue.

Operative Procedure. In 11 patients abdominal exploration only was possible on account of extensive malignancy. In 4 cases cholecystectomy was performed and once posterior gastro-enterostomy for the relief of pyloric obstruction. In the remaining 7 patients the gall-bladder was drained.

Result. Two patients recovered and have remained well longer than four years. Fatal termination followed in the remainder either shortly after operation or within eight months subsequent to leaving the hospital.

THE RELATION OF PAIN IN GASTRIC AND DUODENAL ULCER TO MUSCULAR ACTIVITY OF THE STOMACH.

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Since the discovery by Boldireff of the presence of contractions in the empty stomach and the demonstration by Cannon that these contractions represent the so-called "hunger pangs," the subject of the activity of the fasting stomach has been most thoroughly worked out by Carlson[1] and his associates both for man and animals. The earlier work of Carlson indicated that the sensory evidence of these contractions, carried by way of the vagus

[1] The Control of Hunger in Health and Disease, Chicago, 1916.